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A Systematic Review on the Effect of Magnesium Sulphate Prophylaxis in Pregnant Mothers Diagnosed With Preeclampsia

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Abstract
Background- Most studies agree on the effect of magnesium sulphate in treating eclampsia or controlling convulsion/seizure in pregnancy but controversies still remained on the importance of magnesium sulphate prophylaxis in preeclampsia to prevent eclampsia and other adverse birth outcomes.
Aim- The aim of this review was to assess the effect of magnesium sulphate prophylaxis on preeclamptic mothers in light of disease progression and adverse outcomes.
Methods- A comprehensive computer-based search of the published work was done in, PubMed/MEDLINE, HINARI and Google scholar. Studies that assessed the effect of magnesium sulphate on prevention of eclampsia and maternal and perinatal birth outcomes and published only in English language were included. Studies that reported progression of preeclampsia to eclampsia and the effect of magnesium sulphate on birth outcomes were included. Statistical analyses were performed using Review Manager, version 5.3 (The Cochrane Collaboration) and STATA Version 11. Quantitative data were presented as risk ratios (RR) with 95% confidence intervals (CI) and pooled estimates (summary RR with 95% CI) were calculated using random-effect meta-analysis.
Results- Overall, 28002 mothers with preeclampsia were included and the individual studies were conducted in American, Asian, European and African countries. About 58% of the studies were randomized control trials. Mild preeclamptic mothers who took magnesium sulphate have similar risk of developing eclampsia as compared with the no magnesium sulphate counterparts (RR: 0.9, 95% CI: 0.53-1.54)). On the contrary, severe preeclamptic mothers who took magnesium sulphate have 66% lower risk of developing eclampsia as compared with the no magnesium sulphate counterparts (RR: 0.34, 95% CI:0.23-0.48)).
Conclusion- From this systematic review and meta-analysis it can be concluded that magnesium sulphate prophylaxis provision for mild preeclampsia cases has no value in preventing severe preecalampsia but found to be effective in preventing eclampsia/convulsion in sever preeclampsia cases. It is recommended that magnesium sulphate should not be given to mild and moderate preeclampsia cases in the absence of adequate evidence from randomized controlled trials.
Keywords: magnesium sulphate, preeclampsia/eclampsia, convulsion

INTRODUCTION

Globally, over half a million women die each year from pregnancy related causes signifying that complications of pregnancy and childbirth are the leading cause of death amongst women of reproductive age[1]. Hypertensive disorders of pregnancy (HDP) is one of the leading causes of maternal and perinatal mortality and morbidity [2]. Globally 10% of women have high blood pressure during pregnancy and preeclampsia complicates 2 to 8% of pregnancies[1]. "Preeclampsia," a unique form of hypertension, occurs only during pregnancy characterized by the onset of hypertension and proteinuria, usually during the third trimester of pregnancy[3].

Women with hypertensive disorders of pregnancy should be offered an integrated package of care covering admission to hospital, measurement of blood pressure, treatment, testing for proteinuria and blood tests[4]. Treatment options for HDP vary according to diagnosis, severity, gestational age, the woman's wishes and the consultant's recommendations. There is a general consensus that antihypertensive treatment decreases morbidity and mortality in pregnant women with severe hypertension. Magnesium sulphate is also recommended to use as an anticonvulsant for prevention and treatment of eclamptic patients [5].

Studies showed that Magnesium sulphate is superior in controlling eclamptic fit as compared to other anticonvulsants such as phenytoin and diazepam. Maternal mortality and recurrence of convulsions were reported to be lower in mothers who took magnesium sulphate as compared with those who took other anticonvulsants [6,7, 8].

Maternal effects of magnesium sulphate include, delay of labour progress, respiratory depression, cardiac arrest, flushing, nausea/vomiting, headache, generalized muscle weakness, shortness of breath and loss of motor reflex. Similarly, the Fetal/Neonatal Effects of magnesium sulphate include, lethargy, hypotonia and respiratory depression [3].

Most studies agree on the effect of magnesium sulphate in treating eclampsia or controlling convulsion/seizure in pregnancy but controversies still remained on the importance of magnesium sulphate prophylaxis in preeclampsia to prevent eclampsia and other adverse birth outcomes. There are two arguments in this regard ; the first one recommends keeping magnesium sulphate only for eclampsia to control seizure [9,10]

and the second one recommends providing magnesium sulphate including in mild and moderate cases as a prophylaxis to prevent the occurrence of eclampsia in addition to treating eclampsia [11, 12]. Each of these arguments is supported by the respective justifications. In the first case, the adverse effect of magnesium sulphate is higher than its beneficial effect if it is universally given as a prophylaxis and treatment, so the recommendation is severe cases should stay nearby to the health facilities and if convulsion occurs magnesium sulphate should be given immediately. Supporters of this option claim that even though magnesium sulphate is given, convulsion will occur, so it is good to treat rather than preventing it. In the second case, many cases of eclampsia occur without having severity signs and symptoms; As a result, it is difficult to say eclampsia is the direct progression of severe preeclampsia. In general, it is impossible to predict eclampsia and the better option is giving magnesium sulphate prophylaxis for all types of preeclampsia to prevent ecalampsia.

The aim of this review was to assess the effect of magnesium sulphate prophylaxis on preeclamptic mothers in light of disease progression and adverse outcomes

METHODS

Searching strategy

A comprehensive computer-based search of the published work was done in, , PubMed/MEDLINE, HINARI and Google scholar using the combination of MeSH (for PubMed) and key terms. The bibliographic lists of searched articles were also used to further retrieve other articles. Date restriction was not applied and all possible studies from the inception of the data bases were considered. The search terms include: 'hypertension', 'hypertensive disorders', 'preeclampsia', 'mild/moderate/severe preeclampsia', 'eclampsia', 'convulsion', 'seizure', 'magnesium sulfate', 'magnesium sulphate', 'pregnancy', 'randomized controlled trials'. These terms were combined with the Boolean Logic (AND, OR and NOT) in different possible ways.

Inclusion criteria

We included interventional (randomized control trials and quasi-experimental studies) and observational studies (cohort, case control and case series). Studies that assessed the effect of magnesium sulphate on prevention of eclampsia and maternal and perinatal birth outcomes and published only in English language were included. We included mothers who received magnesium sulphate prophylaxis in the prepartum, intrapartum and postpartum phases and all stages of preeclampsia (mild, moderate and severe) were considered. Only studies comparing magnesium sulphate with placebo or with no magnesium sulphate group were included. We excluded studies where women were given magnesium sulphate for another purpose, such as an adjuvant for anaesthesia or to act as a tocolytic agent. In addition, studies comparing magnesium sulphate with another alternative anticonvulsants were not include

Study selection

Study selection was made in three stages. First titles of articles were retrieved according to search terms and eligible abstracts were identified. Secondly, the eligible abstracts of the retrieved articles were reviewed. Thirdly, all the articles found to be eligible for full document review in the second stage were reviewed in detail. All review processes were made according to the inclusion criteria.

Outcome measures

We included studies that reported progression of preeclampsia to eclampsia and the effect of magnesium sulphate. Thus, primary outcome was eclampsia/progression to severe preeclampsia. Secondary outcomes were postpartum haemorrhage, abruption placenta, caesarean section, respiratory depression, maternal death and baby death/admittance to intensive care nursery.

Data abstraction

After identifying the articles to be reviewed, standardized data abstraction format was developed**.** The data abstraction form included the following information: name of the first author, country of study conducted, study period, study design, total number of participants, the control/comparison, outcome or maternal and perinatal adverse effects reported. The abstraction was conducted by two independent reviewers and when discrepancies observed it was solved by the third reviewer.

Quality (risk of bias) assessment

Methodological quality assessing was made by using Newcastle-Ottawa scale and JADAD criteria for observational studies and randomized control trials respectively. Assessment of statistical heterogeneity among the studies was done by visual inspection of forest plots (i.e. the overlap of the confidence intervals among the studies), Chi-squared (assessing the P-value) and by calculating the I-squared statistic. If the P-value less than 0.10 and I-squared exceeded 50% and visual inspection of forest plots is indicative, heterogeneity was considered to be substantial and reasons for it was sought by doing a subgroup and sensitivity analysis. Additionally, Funnel plots and Egger's regression test was used to search the potential publication bias.

Statistical analysis

Statistical analyses were performed using Review Manager, version 5.3 (The Cochrane Collaboration) and STATA Version 11. For intervention studies we presented quantitative data from individual studies where

possible as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes. Pooled estimates (summary RR with 95% CI) were calculated using random-effect meta-analysis as we considered that there was clinical heterogeneity sufficient to expect the underlying effects differed between trials, or there was substantial statistical heterogeneity (where I^2 was greater than 50% or there was a low P-value, less than 0.10 in the Chi2 test).

RESULTS

Study selection

The initial database searching identified 3025 articles by using the predetermined search terms. From the total retrieved articles 346 were excluded because of duplication in multiple sources. After screening the titles, 275 articles were retrieved for abstract review; 198 articles were excluded after reviewing the abstract. Sixty five articles were excluded after full document review as the objectives of the studies were not related with the interest of the review and at the end 12 articles were included for the final review **(Fig 1).**

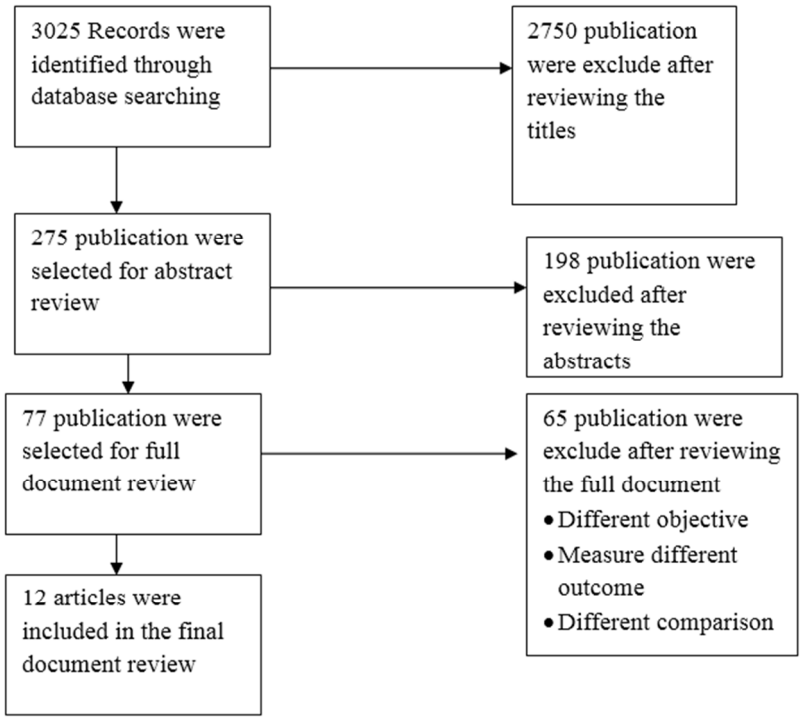

Figure1. Flow diagram showing selection of studies

Overall, 28002 mothers with preeclampsia were included and the individual studies were conducted in American, Asian, European and African countries. About 58% of the studies were randomized control trials; the other types of studies include: one quasi-experimental interventional study, two cohort, one case-control and one case series [**Table 1]**. Two studies reported severe preeclampsia as an outcome[13,14] and three studies reported eclampsia as an outcome [15,16,17]. Three studies reported on postpartum haemorrhage after receiving magnesium sulphate [13,14,18]. Five studies have reported perinatal adverse outcomes in addition to the maternal adverse outcomes [10,12,13,17,19]. The maternal adverse outcomes extracted from the review include: severe preeclampsia, caesarean delivery, chorioamnionitis, postpartum hemorrhage, occurrence of eclampsia, death, placental abruption and duration of labour. Likewise the perinatal adverse outcomes include: apgar scores, neonatal death and still birth. Two randomized control trials (n=357) assessed whether magnesium sulfate prevents disease progression in women with mild preeclampsia and compared the occurrence of severe preeclampsia among mothers who were given magnesium sulphate and placebo. No difference was observed regarding to the progression of mild to severe preeclampsia among the two groups [13,14]. Another three randomized control trials (n=23,350) were conducted to determine whether the administration of prophylactic intravenous magnesium sulphate reduces the occurrence of eclampsia in women with severe pre-eclampsia and in all of the studies women allocated magnesium sulphate had lower risk of eclampsia than those allocated placebo [15,16,17]. Postpartum homerrhaege was reported in three studies as an outcome and in two studies (n=289) the rate of postpartum hemorrhage was higher among preeclamptic women treated with magnesium as compared with those who received no magnesium[14,18], but in one study (n=222, mild preeclampsia cases) there was no difference in the rate of postpartum haemorrhage among the two groups [13].

Table 1. General characteristics of studies included in the review and analysis

SN	Author/s	Year	Country	Study design	Population	Intervention	Control	Outcome
1	Jeffrey C. Livingston, Lisa W. Livingston, Risa Ramsey,	2003	USA	RCT	222 women with mild preeclampsia	Magnesium sulphate	Placebo	• Sever preeclampsia. • Caesarean delivery • chorioamnionitis • postpartum hemorrhage • Apgar scores
2	Coetzee EJ, Dommisse J, Anthony J.	1998	South africa	RCT	685 women with severe pre-eclampsia	Magnesium sulphate	Placebo	• The occurrence of eclampsia
3	Vern L. Katz, Richard Farmer, Jeffery A. Kuller et.al	2000	USA	Retrospective cohort	53 pregnancies complicated by eclampsia	Magnesium sulphate	No treatment	• Progress of severe preeclampsia to eclampsia
4	Magpie Trial Follow-Up Study Collaborative Group.	2007	UK	RCT	3375 preeclamptic mothers	magnesium sulphate	placebo	• Death or serious morbidity at 2 years
5	Chen FP, Chang SD, Chu KK.	1995	Taiwan	RCT	64severe preeclampsia mothers	magnesium sulphate	No treatment	• Development of eclampsia
6	Sara E. Szal, Mary S. Croughan-Minihane, and Sarah J. Kilpatrick,	1999	USA	Retrospective cohort study	154 pregnant women	magnesium sulfate	No Treatment	• Duration of labour • PPH) • Admittance to intensive care nursery
7	Hall D. R. Odendaal H. J. Smith M.	2000	South Africa	Case series	318 preeclamptic women	NA	**NA**	• Eclampsia and related complications
8	Sibai Baha M.	2004	USA	RCT	12673Severe preeclamptic women	magnesium sulphate	placebo	• Convulsion /eclampsia
9	Andrea G. Witlin, Steven A. Friedman, and Baha M. Sibai,	1997	USA	RCT	135 Women with a diagnosis of mild preeclampsia	magnesium sulphate	placebo	• Duration of labour and complications
10	Dima Abi-Said , John F.Annegers, Deborah Combs-Cuntrell et.al	1997	USA	Case-control	66 cases of eclampsia	Magnesium sulphate	control	• Prevention of eclampsia
11	Altman D. Carroli G. Duley L. et.al	2002	UK/33 countries	RCT	9992 preeclamptic mothers	magnesium sulphate	placebo	• Eclampsia and death of the baby
12	Shamsuddin L, Nahar K, Nasrin B, et.al	2005	Bangladish	quasi-experimental study	265cases of eclampsia and severe pre-eclampsia	in intervention group	non-intervention	• Maternal and neonatal adverse Effect

Meta analysis

Five randomized controlled trial studies which had similar outcome of interest were selected for meta-analysis to determine the pooled estimate for severe preeclampsia/eclampsia. As it is depicted in the forest plot, preeclamptic mothers who took magnesium sulphate had 52% lower risk of developing eclampsia as compared with the no magnesium sulphate counterparts (RR:0.48, 95% CI:0.28-0.8)). But the studies are heterogeneous as it can be seen from the I^2=72.2%, so it would be difficult to combine and conclude using the pooled estimate (**Fig.2**).

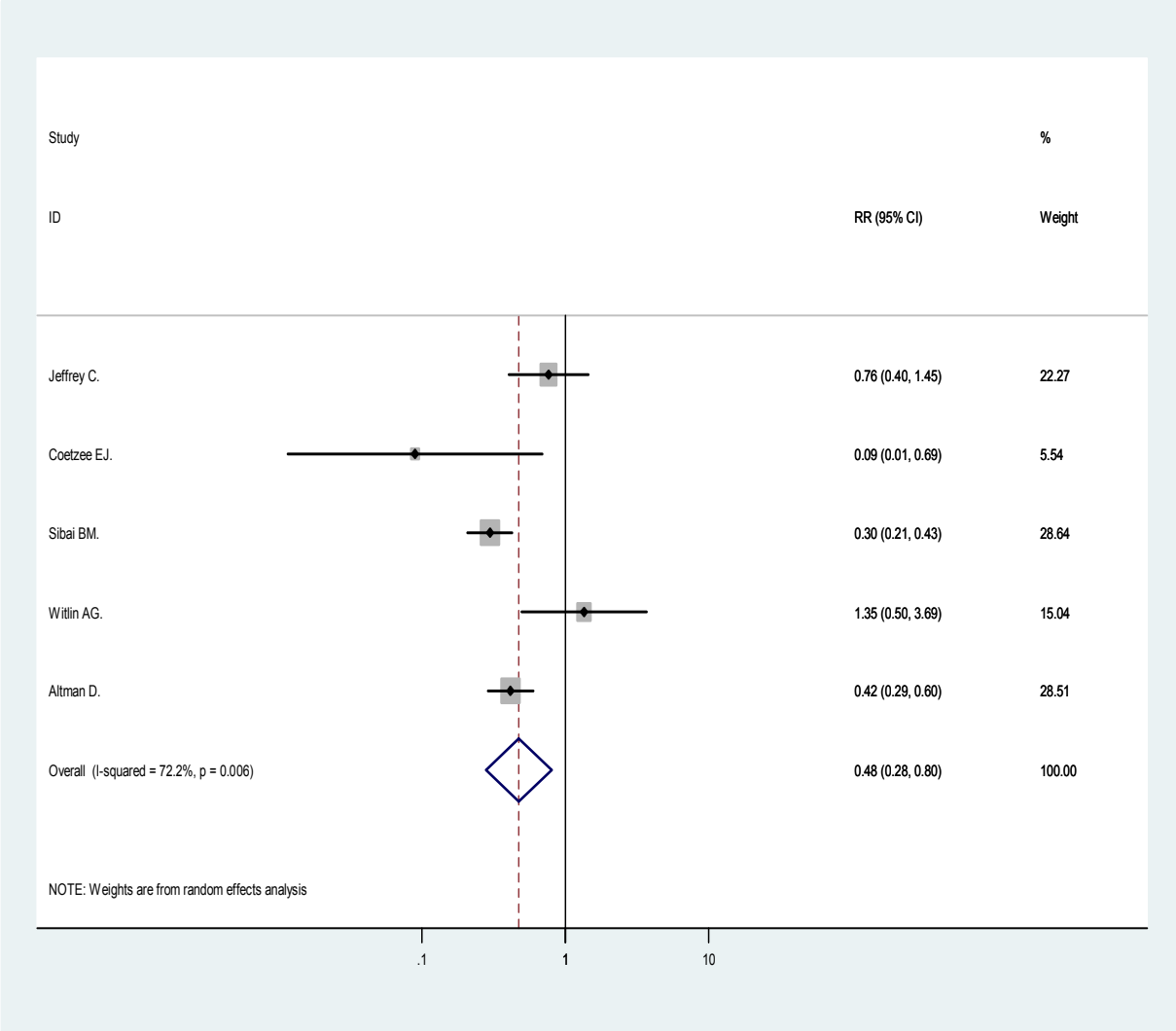

Figure 2. The effect of magnesium sulphate prophylaxis in pregnant mothers diagnosed with preeclampsia (Forest plot)

Subgroup analysis by outcome type

One way of managing heterogeneous studies is by conducting subgroup analysis. In this review there are two outcomes; severe preeclampsia and eclampsia. When we run separately according to the outcome, the respective studies became homogenous (I^2=0.0% for severe preeclampsia) and (I^2=39.8 for eclampsia). In this case it is possible to combine the studies. As it is depicted in the forest plot in Fig.3 (subgroup analysis), mild preeclamptic mothers who took magnesium sulphate have similar risk of developing eclampsia as compared with the no magnesium sulphate counterparts (RR: 0.9, 95% CI: 0.53-1.54)). On the contrary, severe preeclamptic mothers who took magnesium sulphate have 66% lower risk of developing eclampsia as compared with the no magnesium sulphate counterparts (RR: 0.34, 95% CI:0.23-0.48)) **(Fig.3).**

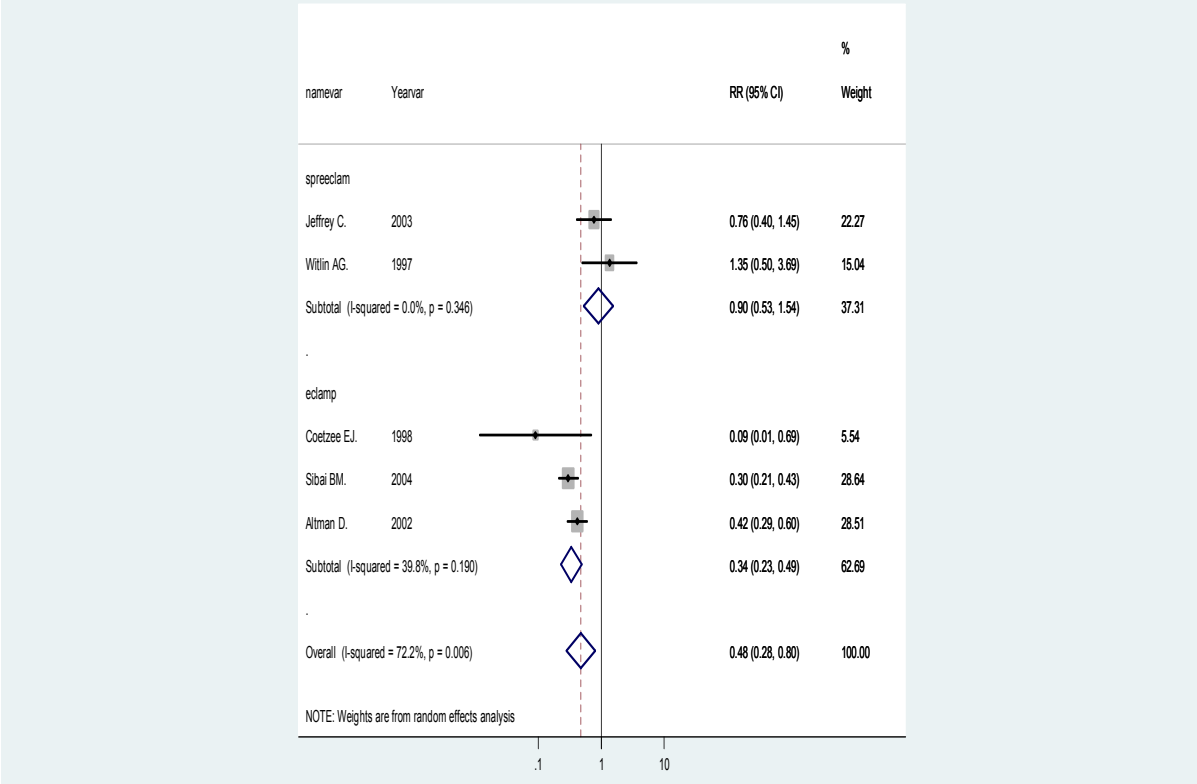

Figure 3. The effect of magnesium sulphate prophylaxis in pregnant mothers diagnosed with preeclampsia (Subgroup analysis)

Test for publication bias

Looking for funnel plot asymmetry is one method of checking publication bias but graphic way of checking publication bias is recommended when there are more than ten studies, so in this case funnel plot **(Figure 4)** is not the appropriate way of checking publication bias as the number of studies reviewed are limited(n=5). To resolve this problem test for statistical significance funnel plot asymmetry was considered which is given by the Egger test which shows no publication bias (p=0.62)

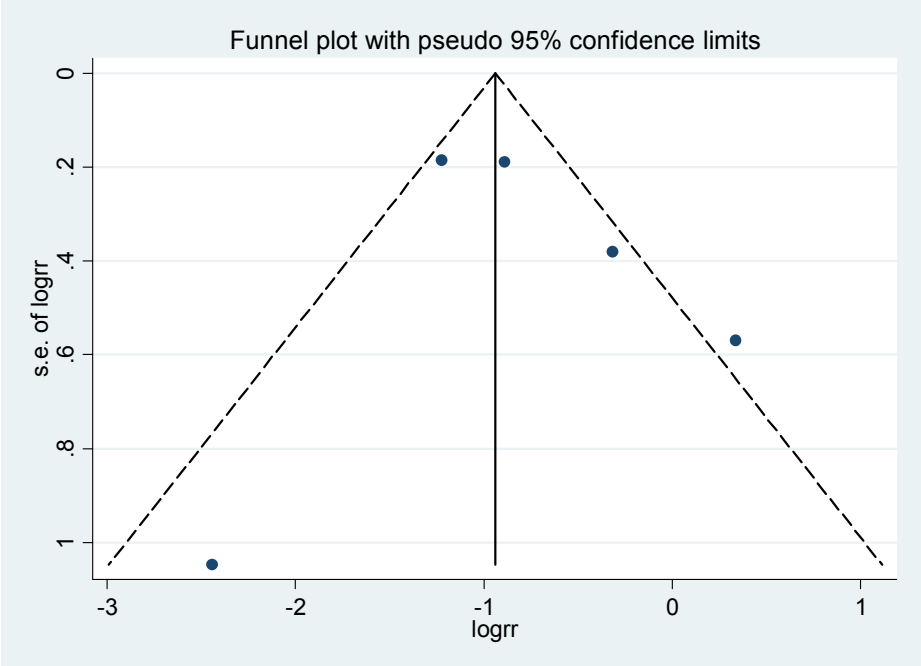

Figure 4. Funnel plot to check publication bias for the effect of magnesium sulphate on preeclampsia

Sensitivity analysis

Sensitivity analysis helps to determine whether individual studies are affecting the overall estimate. If there is single study affecting the overall review, it means that the review is sensitive. If the individual studies are not affecting the overall estimate it means that the review is not sensitive. As it can be seen from figure **5,** whenever each study is removed the pooled estimate, doesn't vary much (**0.48**)

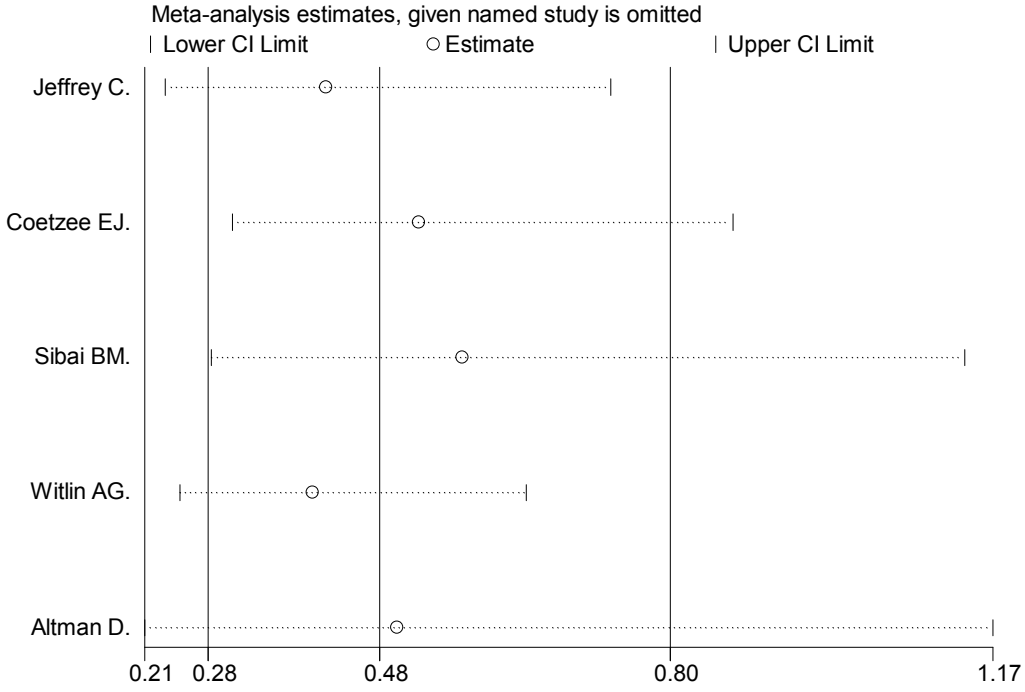

Figure 5. Sensitivity analysis for the effect of magnesium sulphate on preeclampsia

Discussion

A systematic review and meta-analysis was conducted to assess the effect of magnesium sulphate prophylaxis on preeclamptic mothers in light of disease progression and adverse outcomes. In this review magnesium sulphate prophylaxis was found to be protective against eclampsia development when given to severe preeclampsia cases which is congruent with the WHO recommendation of providing magnesium sulphate prophylaxis for severe preeclampsia and eclampsia cases [20]. On the other hand, according to this review magnesium sulphate prophylaxis has no effect in the prevention of disease progression in mild preeclampsia cases, in contrary to this finding; a systematic review on descriptive studies by Brhane Y. revealed that a significant number of eclamptic women had either normal blood pressure or mild-to-moderate hypertension immediately before seizure which means the findings were in support of initiating magnesium sulfate prophylaxis to all women with mild pre-eclampsia[11]. The discrepancy may be due to the difference in the study designs; the current review pooled two randomized control trial results but the previous review qualitatively summarized descriptive studies. This review implies that there are only limited randomized control trials conducted so far to assess the effect of magnesium sulphate on mild preeclampsia cases suggesting the need to have large randomized control trials to investigate the case.

In the current systematic review, the reviewed studies reported that mothers having severe preeclampsia and given magnesium sulphate prophylaxis had higher chance of developing postpartum haemorrhage as compared with those who were given no magnesium sulphate prophylaxis. This shows, though the exact mechanism of magnesium sulphate is unknown it has tocolytic effect (relaxes the uterus) which leads to poor contraction in the postpartum period which may in turn lead to severe postpartum haemorrhage [21].

In the current review magnesium sulphate prophylaxis was found to be associated with some adverse outcome (PPH) but no difference observed in other maternal and perinatal adverse outcomes. In other literatures postpartum hemmorhage is not frequently described as adverse outcome of magnesium sulphate a part from respiratory depression and weakening of reflexes which implies less emphasis given to this part. Cognizant to the serious consequences of postpartum hemmorhage this study revealed the important causations to be taken in to consideration while providing magnesium sulphate as a prophylaxis and treatment for severe preeclampsia and eclampsia cases respectively.

Strength and limitations

Strength

- Majority of the studies reviewed are randomized controlled trials and it covers large sample size.

Limitations

- Only articles published in English language were considered
- Unpublished/grey literature were not included

Conclusion

From this systematic review and meta-analysis it can be concluded that magnesium sulphate prophylaxis provision for mild preeclampsia cases has no value in preventing severe preecalampsia though the studies reviewed are limited to reach in a plausible conclusion. On the other hand magnesium sulphate prophylaxis given for sever preeclampsia is found to be effective in preventing eclampsia/convulsion. Health professionals should keep magnesium sulphate for severe preeclampsia and eclampsia cases only and they should be aware of the adverse effects of magnesium sulphate especially post partum haemorrhage while providing the drug for prevention and treatment purposes.

Competing interests

The authors declare that we have no competing interests.

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